**A Phase I/II clinical trial of pNGVL4a-Sig/E7(detox)/HSP70 for the treatment of patients with HPV16+ Cervical Intraepithelial Neoplasia 2/3 (CIN2/3)**

## Scientific Abstract


### Background
Cervical cancer is the third leading cause of cancer death in women worldwide. In the United States, despite the availability of inexpensive, noninvasive screening, cervical cancer remains the sixth most commonly diagnosed malignancy among women. Over the past decade, SEER[1] data have demonstrated a 17% increase in incidence in the U.S., normalized for population growth, with a disproportionate increase among young women. Current primary therapies include radical surgery and chemoradiation. For those with recurrent disease, a combination of further surgery including total pelvic exenteration, radiation, and chemotherapy may be used. However these modalities are associated with significant treatment toxicity, and overall survival remains a dismal 40%. One of the best strategies to decrease the disease burden of cervical cancer is to intervene in patients with premalignant disease of the cervix. The identification of the association of high-risk strains of human papillomavirus (HPV) with premalignant disease of the cervix provides an ideal opportunity to develop vaccines targeted at HPV+ premalignant lesions. HPV16 is associated with over half of all cervical cancers and precursor lesions (CIN2/3). The DNA vaccine we propose to evaluate, pNGVL4a-Sig/E7(detox)/HSP70, is targeted at the HPV16 E7 protein, which is consistently expressed in cancerous and precancerous epithelial cells, but not in normal tissue.

### Objectives
1) To identify and characterize toxicities in a phase I clinical trial of DNA vaccination with pNGVL4a-Sig/E7(detox)/HSP70 in healthy women with HPV16+ CIN2/3; 2) to identify the best dose of this vaccine in this patient cohort, based on tolerability and evidence of immune response, 3) to estimate the association of specific in-vivo parameters of immune response with clinical response.

### Patient Population
Thirty-one healthy women with colposcopically directed biopsy confirmed CIN2/3, caused by HPV16.

### Study Design
Open label rapid dose-escalation with an expanded cohort at the highest safely tolerated dose.

### Treatment Plan and Schedule
Following routine diagnostic workup of CIN2/3, patients will receive a total of three vaccinations with the study vaccine, pNGVL4a-Sig/E7(detox)/HSP70, at monthly intervals. Patients will undergo interval colposcopy at week 8 to ensure that lesions are not increasing in size or severity. Patients will undergo standard therapeutic resection of the affected cervical tissue at study week 15.


[1] SEER: Surveillance, Epidemiology and End Results

**Dose**
The vaccine will be administered as an intramuscular injection in the deltoid muscle, at weeks 0, 4, and 8. There are three dose levels in the dose ranging portion of the clinical trial; 500, 1000, and 3000 µg. The 500 µg dose will be the starting dose. Each patient will be sequentially assigned to open treatment positions in the study. Accrual to the study will continue until every treatment position is evaluated, or dose limiting toxicities are observed.

There will be a two-week stagger between dose groups to allow for the assessment of safety and tolerability before proceeding to the next higher dose. No dose-limiting toxicities have been observed at any dose level of DNA vaccination in the literature.

**Dose-limiting toxicity**
Dose-limiting toxicity (DLT) is defined as any grade 3 or 4 adverse event as defined in the NCI Common Toxicity Criteria v3.0. If a DLT occurs, treatment will be stopped. Treatment may be restarted if the DLT resolves to <grade 2. To begin a dose level, three patients will be given treatment at weeks 0, 4, and 8. If none of the three has a dose-limiting toxicity (DLT), then we will progress to the next dose level. If two or three of the patients have a DLT, then we will de-escalate to the previous level and treat three more patients if six have not been treated already at that level. If exactly one of the three has a DLT at a particular dose, then three more patients will be given the same dose for a total of six patients. If the 3000 µg dose level is attained and the first three patients exhibit no DLTs, then another three patients will be given the 3000 µg dose. If one or fewer have DLTs out of six, then level 3000 µg will be designated as the µg MTD. No more than six patients will be enrolled at either of the first two levels.

**Safety Evaluation**
The toxicity data will be descriptive, characterized according to the NCI CTC v3.0. Monitoring for adverse events will occur internally on real time, at regular, weekly meetings of the Johns Hopkins Oncology Center Clinical Trials Working Group, and annually, by the Hopkins Oncology Center Clinical Research Review & Monitoring Committee.

**Product**
The vaccine, pNGVL4a-Sig/E7(detox)/HSP70, is a DNA vaccine targeted at the Human Papillomavirus (HPV) 16 E7 antigen, for the treatment of patients with high grade, pre-invasive HPV16 intraepithelial lesions (HGSILs) of the cervix. The vaccine is composed of a naked plasmid DNA vector, pNGVL4a, into which the antigen of interest, HPV16 E7(detox), linked to targeting sequences which enhance the potency of intramuscular (IM) DNA vaccination, namely, signal peptide (Sig), and mycobacterium tuberculosis heat shock protein 70 (HSP70), has been cloned. Clinical grade drug has been manufactured via the NCI RAID mechanism.